

# Noninvasive Multi-echo Vessel-Encoded Arterial Spin Labeling Reactivity for More Comprehensive Quantification of Hemodynamic Compensation: Development and Clinical Implementation in 50 Patients with Cerebrovascular Disease

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**Target Audience:** Basic scientists and stroke clinicians with an interest in development and implementation of hemodynamic MRI methods with prognostic potential.

**Purpose:** The purpose of this work is to develop and clinically implement a noninvasive MRI protocol for quantifying the relationship between key hemodynamic compensation mechanisms including cerebrovascular reactivity (CVR), baseline cerebral blood flow (CBF), CBF reactivity, and CBF territory dynamics in patients with cerebrovascular disease. Despite progress in stroke treatment, 20-30% of strokes result in death within one month and 70-80% result in significant long-term disability. Reducing stroke-related morbidity ultimately requires an improved understanding of early markers that predict hemodynamic collapse and better identification of patients requiring aggressive, preventative therapy. Specifically, in many patients at risk for stroke with compromised cerebral perfusion pressure, the extent of hemodynamic compromise reflects the autoregulatory capacity of vasculature to increase arterial cerebral blood volume and/or develop collaterals to supplement CBF. However, the critical barrier to stratifying stroke risk based on this information rests with a lack of (i) methodology for measuring multiple hemodynamic parameters in a clinically relevant timeframe and (ii) knowledge of how changes in such parameters should be interpreted for prognosis. To address these gaps in our knowledge, we have proposed a multi-echo (ME) adaptation of the vessel-encoded arterial spin labeling (VE-ASL) approach<sup>1-3</sup> that allows for quantification of CVR, baseline CBF, and CBF territory mapping. This 15 min protocol is implemented clinically in a major university hospital and results are presented from 50 clinical scans. Technical hypotheses regarding the efficacy of using gas delivery challenges and ME VE-ASL for determining reproducible CVR in a clinical setting, and more clinical hypotheses regarding relationships between compensatory hemodynamic measurements and (i) clinical measures, (ii) changes following revascularization, and (iii) symptomatology are evaluated.

**Methods:** 50 (17M/33F; age=50±19 yrs) scans were performed at 3T (Philips) on adult patients and study volunteers with varying cerebrovascular disease etiology, including patients with Moyamoya disease (n=20), cervical steno-occlusion (n=10), intracranial stenosis (n=13), cognitive impairment (n=5), and other vasculopathies (n=2). All participants provided informed, written consent. Changes in end-tidal CO<sub>2</sub> ( $\Delta EtCO_2$ ) were monitored and CVR was assessed using blood oxygenation level-dependent (BOLD) MRI (TR/TE=2000/35 ms; spatial resolution = 3.5x3.5x3.5 mm<sup>3</sup>) in conjunction with 180s/180s off (room air) / on (5%/95% CO<sub>2</sub>/O<sub>2</sub>) breathing. Baseline CBF was assessed using a pseudo-continuous (pCASL) approach (TR/TE=4000/1650/13 ms; spatial resolution = 3x3x7 mm<sup>3</sup>). 10 patients underwent an adapted protocol whereby a ME VE-ASL (TR/TE1/TE2=4500ms/13ms/35ms) approach with five planning-free labeling geometries<sup>3</sup> was employed during the hypercarbia paradigm. Labeling geometries corresponded to control (no labeling), label (all inflowing vessels), right internal carotid artery (RICA), and two schemes for vertebralbasilar artery (VBA). Data were corrected for baseline drift, motion, and co-registered to native (T<sub>1</sub>) and standard (MNI 2 mm)

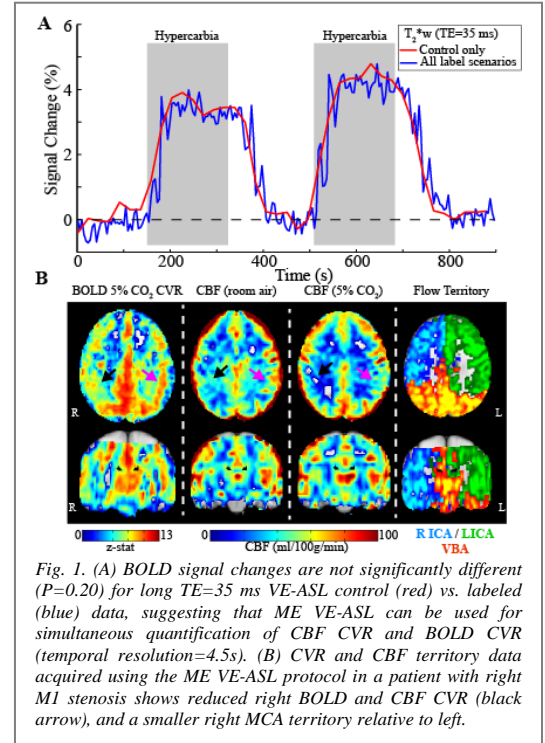


Fig. 1. (A) BOLD signal changes are not significantly different ( $P=0.20$ ) for long TE=35 ms VE-ASL control (red) vs. labeled (blue) data, suggesting that ME VE-ASL can be used for simultaneous quantification of CBF CVR and BOLD CVR (temporal resolution=4.5s). (B) CVR and CBF territory data acquired using the ME VE-ASL protocol in a patient with right M1 stenosis shows reduced right BOLD and CBF CVR (black arrow), and a smaller right MCA territory relative to left.

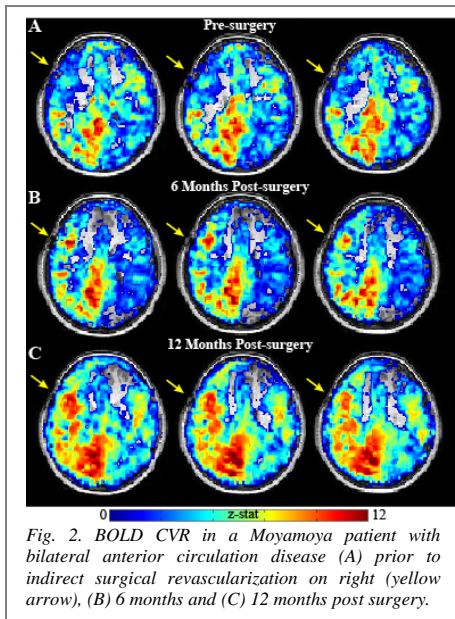


Fig. 2. BOLD CVR in a Moyamoya patient with bilateral anterior circulation disease (A) prior to indirect surgical revascularization on right (yellow arrow), (B) 6 months and (C) 12 months post surgery.

space. For BOLD, z-statistics and signal changes normalized by  $\Delta EtCO_2$  were recorded. For ASL, CBF was quantified upon application of the flow-modified Bloch equation, accounting for labeling duration and magnetization transfer effects. In ME VE-ASL, BOLD analysis was performed on TE<sub>2</sub>=35 ms control data and TE<sub>2</sub>=35 ms labeled data to understand to what extent  $\Delta M_z$  contributions contribute to the primarily  $\Delta M_{x,y}$  weighting for each labeling condition. CBF territory maps were calculated using a k-means clustering approach from TE<sub>1</sub>=13 ms data<sup>3</sup>. Moyamoya MRI hemodynamic data were compared with clinical disability scores and modified Suzuki Scores (mSS), calculated from digital subtraction angiography (DSA).

**Results and Discussion:** 94% of participants completed CVR scans.  $\Delta EtCO_2$  was 5.9 ± 1.9 mmHg (n=47); over this range, a non-significant relationship between  $\Delta EtCO_2$  and cortical BOLD CVR was observed ( $R^2=0.07$ ;  $P=0.07$ ), suggesting that small inter-subject  $\Delta EtCO_2$  variability from a standard pre-mixed clinical gas delivery setup does not contribute significantly to CVR variability on average. At TE<sub>2</sub>=35 ms, the spin labeling contributes minimally ( $\Delta M_z=0.004$ ) relative to BOLD weighting ( $\Delta R_2^*=-0.74s^{-1}$ ;  $\Delta M_{x,y}=0.026$ ). This small effect was confirmed experimentally, when the TE<sub>2</sub>=35 ms VE-ASL data were analyzed using all five labeling scenarios vs. only the control scenario (Fig. 1). This finding demonstrates that moderate temporal resolution (TR=4500 ms) can be achieved for BOLD sensitivity in a functional ME VE-ASL approach. Clinical findings varied with underlying etiology. For instance, in patients with Moyamoya disease, mean z-statistics demonstrated that BOLD CVR was significantly ( $P=0.017$ ) higher in low mSS hemispheres (z-statistic=5.0±2.5) compared to high mSS hemispheres (z-statistic=3.7±1.7), implying that regions with less advanced stages of Moyamoya disease have higher reactivity. Opposite relationships ( $P<0.05$ ) between BOLD time-to-peak and arterial circulation time (ACT), and CBF and ACT, demonstrate that BOLD and ASL contrasts correlate with DSA measures of vascular compromise. Clinical symptomatology correlated with regional negative BOLD CVR: of the Moyamoya subjects demonstrating regional negative BOLD CVR (n=5), four presented with lateralizing clinical symptoms. As part of an ongoing study, all study participants are monitored longitudinally to understand the relationship between surgical revascularization (Fig. 2), more conservative medical management, and stroke risk.

**Conclusion:** A clinical 3T head MR protocol was expanded to include simultaneous measurements of CVR, baseline CBF, CBF reactivity, and CBF territory mapping using a novel 15 min ME VE-ASL approach. This approach was implemented in 50 patients and results illuminated impairment not clear from structural imaging.

**References:** <sup>1</sup>Wong EC. MRM. 2007 Dec;58(6):1086-91. <sup>2</sup>Okell TW et al. MRM. 2012 Sep;68(3):969-79. <sup>3</sup>Gevers S et al. AJNR. 2012 Feb;33(2):E21-5.